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14. ABSTRACT
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Results: In teeth with or without a preoperative PARL, EMS resulted in a statistically significant difference in complete healing (49/57 or 86.0%) versus retreatment (28/68 or 41.2%) with $P<0.0001$. EMS resulted in a statistically significant difference in combined complete healing and reductive healing (54/57 or 94.7%) versus retreatment (56/68 or 82.4%) with $P = 0.035$.

Of 46 recalls in which CBCT detected a PARL, PA detected 30 (35% PA false negative rate). Of the 79 recall studies in which CBCT did not detect a PARL, PA did detect PARL in 13 (16.5% PA false positive rate).
Conclusions: In this CBCT and clinical data-based outcomes assessment EMS resulted in greater mean volumetric reduction and a higher healing rate compared to retreatment. Post-operative CBCT is more sensitive and specific than PA in assessing PARL and has demonstrable utility in outcomes assessment.

Introduction:

Apical periodontitis occurs as bacterial infection of the root canal system activates the host immune response. Endodontic treatment aims to eradicate and entomb bacteria, precluding interaction with periradicular tissues, resulting in regeneration or repair of the affected site (1-3). Healing of apical periodontitis can be initiated by root canal therapy, retreatment, endodontic surgery, or extraction, and is evidenced by normal function, absence of clinical signs and symptoms and radiographic presentation of osseous regeneration with reestablishment of a periodontal ligament space.

Two-dimensional PA are the most commonly used imaging technique for endodontic outcomes assessment; they detect lesions when there is perforation of the cortical plate or erosion of the inner or outer surface of the cortex (4). Lesions that are confined to the cancellous bone may not be detected by PA. Further, limitations in lesion detection with PA occur because of geometric distortion and superimposition of several radio-densities of bone and soft tissue at various depths, into one planar image. The clinician is then required to "interpret" this planar summation of radio-densities, factoring in the possibility of geometric distortion, prior to determining an outcomes assessment. Often, this has the effect of inaccurate lesion size interpretations and false negative and less commonly false positive designations (5,6).

Historical studies using 2 dimensional x-ray interpretations show that it may take up to 4 years for healing to occur following root canal therapy (7). A four-year observation period following endodontic surgery in cases demonstrating uncertain healing has been proposed (8). Radiographic designations for osseous healing after endodontic surgery have classically been divided into four groups: complete healing, incomplete healing, uncertain healing, and unsatisfactory healing (9). Recall examinations over a four-year period do not always occur. More sensitive and specific three-dimensional imaging measures might provide a more clear and timely patient-centered outcomes assessment.

CBCT utilizes x-ray beams to acquire multiple images that render a 3-D representation of the teeth and surrounding tissues. Tissue can be analyzed in axial, coronal, and sagittal views. Recent evidence indicates an enhanced diagnostic ability of CBCT over two-dimensional radiography in the detection of periapical lesions, as seen in Figure 1 (10-16). Mota de Almeida et al. found that treatment plan alterations were attributed to CBCT in 53% of referred endodontic patients in which a pre-operative CBCT was acquired (17). Ee et al. reported endodontic treatment plan alterations occurred in 62.2% of cases after CBCT imaging, versus PA alone (18). Rodriguez et al. concluded: "CBCT imaging has a substantial impact on endodontic decision making among specialists, particularly in high difficulty cases" (19). CBCT images can be imported into specialized imaging software for PARL volume rendering based on detailed tracings. This method might overcome interpretation error inherent with two-dimensional PA alone, specifically the presence or absence of osseous healing or healing trends. Counter arguments suggest that the ultimate benefit of CBCT in endodontics is unclear and its routine use for detecting periapical radiolucencies is not justified (20, 21).

Given potential gains in sensitivity and specificity in outcomes assessment, studies incorporating CBCT pre-operatively and at recall are warranted. A gap in knowledge is illustrated by cases where an outcome seems unclear based on PA alone but becomes clear with CBCT. Recent studies have found that post-op CBCT yields a less favorable outcome assessment versus PA alone for initial root canal treatment, retreatment, and EMS (22,23,24). The question is: should CBCT routinely be employed in assessment of post-operative outcomes?

The aim of this study was to retrospectively assess treatment outcomes for retreatment and EMS through clinical assessment, and a CBCT-based calculation of volumetric change. The study also compares examiner PA interpretations with examiner CBCT findings in identification of PARL.

Materials and Methods:

Potential subjects were retrospectively identified using a database containing all patients who were at least 18 years of age and who had received retreatment or EMS at Wilford Hall Ambulatory Surgical Center Endodontics Residency between 1 July 2011 and 31 July 2015. Patients whose treatment included pretreatment PA and CBCT imaging and who returned for a recall examination (range of 12-53 months) with PA and CBCT imaging were included in the study. Criteria were met by 125 teeth of 97 patients: 68 retreatments and 57 EMS treatments. The mean patient age was 47.7 years with a range of 19-86 with 54 men and 43 women. A retrospective treatment outcomes assessment was conducted based upon clinical and CBCT (instead of PA) findings. The 59th Medical Wing Institutional Review Board approved the protocol.

Treatment Protocol

Treatments were completed by endodontic residents under the supervision of board-certified Endodontists. Retreatment and EMS were completed using a dental operating microscope (Zeiss OPMI PROergo) and contemporary materials and techniques. Retreatment protocol involved use of a rubber dam, 6-8.25% NaOCl, 17% EDTA, 2% Chlorhexidine, $Ca(OH)_2$ inter-appointment dressing for a minimum 7 days as deemed necessary by the provider, gutta-percha and Roth's Sealer, and bonded orifice barriers. Apical surgery protocol involved full thickness mucoperiosteal flap reflection, osteotomy preparation and root-end resection, ultrasonic preparation and root-end fillings with gray or white ProRoot MTA (Dentsply, Tulsa, OK) or EndoSequence BC Root Repair Material (Brassler USA, Savannah, GA). Nine osteotomy sites were grafted with Calcium Sulfate and OraGraft DFDBA and one site was grafted with Geistlich Bio-Oss Collagen®. No membranes were used.

A 3D Accuitomo 170 (J. Morita USA, Irvine, CA) generated CBCT scans with 60x60mm or 40x40mm fields of view at 90 kVp and 5-9 mA. All pre-operative and post-operative periapical images were taken utilizing a paralleling technique and external cone positioning device (XCP) using size 2 digital sensors (Kodak RVG 6100). A dental x-ray machine (Planmeca Intra, Helsinki, Finland) was used to expose the sensors with adjustable kVp, mA, and time settings dependent upon patient size and location in the oral cavity.

Clinical Data Collection & Interpretation

De-identified pre-operative and recall clinical data was entered into a secure digital file. A random sequence generator was used to assign each patient a number such that the clinical data obtained from patient records could be matched with corresponding radiographic imagery. Pre-operative variables that were analyzed included: presence of pain, percussion and palpation findings, probing depths, presence of a sinus tract and presence of un-instrumented canals. Intraoperative variables analyzed included: grafting materials (when used) and root-end filling and obturation materials. Recall variables analyzed included: presence of pain, percussion and palpation tenderness, probing depths, or the presence of a sinus tract.

Examiner Calibration and Radiography and analysis

De-identified patient CBCT scans (125 pre-op and 125 recall) were imported into specialized imaging software (Amira 5.3.4, Visage Imaging GmbH, Berlin, Germany) for analysis by two board-certified Endodontists. During tracing of PARL borders, examiners constantly discussed and reached consensus on border designations. A minimum of 7 individual circumferential tracings at various locations on the borders of the PARL were utilized by specialized imaging software for volume rendering. If the 3-D rendering did not intimately conform to the anatomy of the PARL, as in lesions with aberrant borders, additional tracings were conducted until intimate conformity was achieved.

In order to assess variability in volumetric measurements, eighteen CBCT scans (9 Pre-op, 9 recall) with PARL of varying sizes were retraced 30 days after initial tracing. Variability was calculated for five size groups (two of which overlapped) based on volume, and a two-sided 95% confidence limit (CL) was calculated for each group (Table 1). The CL was applied to all volumetric measurements when determining if post-op volumes changed relative to pre-op volumes. Based on the 95% CL for measurement in the 0-10mm^3 range, a volume measuring less than or equal to 3.6 mm^3 was designated as no PARL.

Of the total 250 scans evaluated, 100 were determined to have a low density area $\leq$ 3.6 mm^3 (no PARL designation). For the remaining 150 scans PARL volumes from >3.6 mm^3 up to 1,449.13 mm^3. Pre-operative and post-operative PARL volumes, percent change in volume, and mean volume change for both EMS and retreatment were calculated.

Examiners used MiPACS dental enterprise viewer (LEAD Technologies Inc, Charlotte, NC) to interpret randomized pre-operative and recall digital PA. The presence or absence of a periapical radiolucency was defined as at least one radiolucency $\geq$ 2 times the width of the PDL space and was determined by consensus. If disagreement occurred between examiners with regards to the presence or absence of a PARL, the stricter interpretation (radiolucency present) was accepted. PA interpretations were not utilized in outcomes assessment. Rather, the number of PARL identified with CBCT was compared to the number identified with PA to determine how often agreement existed.

Assessment of Healing

Pre and post-operative clinical findings were matched with CBCT PARL volumetric changes in determining outcomes assessment. Complete healing was defined as absence of pain, absence of percussion and palpation tenderness, no probings indicative of endodontic failure, and periapical lesion volume $\leq$ 3.6 mm^3. Reductive healing was defined as absence of pain, absence of percussion and palpation tenderness, no probings indicative of endodontic failure, and a PARL that reduced in volume but was $\geq$ to the CL volume of 3.6mm^3. Failure was defined as

presence of pain, percussion or palpation tenderness, probings indicative of endodontic failure, or a periapical lesion volume that remained unchanged or increased in volume.

Results:

The mean follow-up period for retreatment was 22 months (range of 12-53 months) and for EMS cases was 23 months (range of 12-41 months). The combined mean follow-up period for the study was 22.3 months (Fig. 2).

Retreatment volumetric changes

Fifty-nine retreatment teeth had a pre-operative PARL; at recall 52/59 or 88.1% of PARL reduced in volume, 2/59 or 3.4% remained unchanged, and 5/59 or 8.5% increased in volume (Fig. 3*A*). Average volumetric change was calculated by adding all of the percentage volume changes for each tooth then dividing by the total number of teeth. For example, a pre-operative PARL with a volume of 100 mm^3 that reduced to a final volume of 50 mm^3 at recall (50% reduction), was weighted equally with a PARL that reduced from 10 mm^3 to 5 mm^3. The average volumetric change was 62.4%. All 9 teeth with no pre-operative PARL did not have a recall PARL (Fig. 3*B*).

EMS volumetric changes

Forty-five EMS teeth had a pre-operative PARL; at recall 44/45 or 97.8% of PARL reduced in volume and 1/45 or 2.2% remained unchanged (Fig. 3*A*). The average volumetric reduction among these PARL was 95.0% (Fig. 3*C*). All 12 teeth with no pre-operative PARL remained unchanged at recall.

Retreatment healing compared to EMS healing

Combining clinical data and CBCT, 21/59 or 35.6% of retreatment teeth with a pre-operative PARL showed complete healing; 28/59 or 47.5% had reductive healing, and 10/59 or 16.9% failed (Fig. 3*D*). For EMS teeth with a pre-operative PARL, 38/45 or 84.4% showed complete healing; 5/45 or 11.1% had reductive healing, and 2/45 or 4.4% failed (Fig. 3*D*).

In teeth with a pre-operative PARL, EMS resulted in a statistically significant difference in complete healing of 38/45 or 84.4% versus retreatment's 21/59 or 35.5% ($P<0.0001$); further, when combined reductive healing and complete healing was considered, EMS showed a statistically significant rate of 43/45 or 95.6% versus retreatment 49/59 or 83.1% ($P = 0.048$).

In teeth without a pre-operative PARL, 7/9 or 77.8% of retreatment teeth showed complete healing, and 11/12 or 91.7% of EMS teeth had complete healing; failure was observed in 2/9 or 22.2% of retreatment cases and 1/12 or 8.3% of EMS cases. All of these failures were related to the presence of clinical signs or symptoms at recall; a PARL did not develop in any of these cases.

Considering all teeth (with or without a pre-operative PARL), EMS resulted in a statistically significant difference in complete healing of 49/57 or 86.0%, versus retreatment's 28/68 or 41.2% ($P<0.0001$). EMS resulted in a statistically significant difference in combined reductive healing and complete healing (94.7%) versus retreatment's (82.4%) with $P = 0.035$.

Periapical radiograph compared to CBCT in detection of recall PARL

Of the 39 recall retreatment cases in which CBCT detected a PARL, PA detected 28 or 72% (PA false negative rate of 28%). Of the 7 recall EMS cases in which CBCT detected a PARL, periapical radiographs detected a PARL in 2 or 29% (PA false negative rate of 71%). Taken together, of 46 recall teeth in which CBCT detected a PARL, PA detected only 30 or 65% (PA false negative rate of 35%). Additionally, of the 50 recall EMS cases in which CBCT did not detect a PARL, PA detected a PARL in 7 (PA false positive rate of 14%). Of the 29 recall retreatment cases in which CBCT did not detect a PARL, PA detected a PARL in 6 (PA false positive rate of 20.7%). In these cases where CBCT did not detect PARL but PA did, osseous healing occurred at the root end but a thin or absent cortical plate or less opaque new trabecular bone gave the impression of a PARL with PA.

Clinical findings as predictors of PARL volumetric changes

None of the pre-operative variables (presence of pain, percussion or palpation tenderness, probing depths greater than 4mm, presence of a sinus tract or missed canals) or intraoperative variables (presence and type of graft material and type of root-end filling or obturation material) were predictive of PARL volumetric change ($P>0.05$).

Discussion:

CBCT exhibits greater sensitivity than digital radiography in the detection of periapical lesions (10-16). In this study, periapical radiographs detected a recall PARL in only 30/46 retreatment and EMS cases in which CBCT detected a PARL. Thus, if CBCT had not been utilized, 34.8% of recall PARL would have gone undetected. In a twenty-year analysis of biopsied radiolucent jaw lesions, only 21/3,626 or 0.6% of inflammatory lesions were scar tissue (27). Likewise, a histological evaluation of persistent periapical lesions associated with nonsurgical endodontic treatment failures yielded a diagnosis of scar tissue in only 2.2% of cases (28). Thus, use of 2-D radiography might support a false notion that complete healing has occurred when it has not, making future recall visits less likely to take place.

Combining CBCT with volume rendering capability adds a new dimension to outcomes assessment by providing quantification of PARL volumetric changes. Bender and Seltzer showed that digital radiography detects lesions in cortical bone only when there is perforation of cortical plate, or erosion of the inner or outer surface of the cortex (4). Orstavik showed that apical healing might take four years following root canal therapy (7). In this study, when examiners disagreed on presence or absence of PARL, the more inclusive "PARL present" designation was made. Even so, PA exhibited less sensitivity in identifying PARL than did CBCT. Our findings indicate that changes in cancellous bone may be occurring after treatment, with inadequate detection by PA alone. Post-operative CBCT could influence treatment decisions in these situations. For example, a CBCT scan taken one year after retreatment that shows an increase in PARL volume (predominately involving demineralization of cancellous bone), could be appropriately treatment planned for apical surgery even when the lesion appears unchanged via two-dimensional radiography. Conversely, the decision to forgo endodontic intervention may be influenced in similar circumstances in which CBCT indicates a volumetric reduction in the PARL. In either case, a pre-operative and post-operative CBCT scan would be required for such a detailed comparison. To our knowledge volume rendering capability is not incorporated into commercially available CBCT software. Future CBCT units that incorporate automated PARL tracing software could make outcome assessment more objective and accurate.

Of the 79 cases in which CBCT indicated no recall apical lesion, 13 (16.5%) PARL were identified using PA. This might be in part due to variability in the detection of very small lesions with CBCT and Amira imaging software. The confidence limit for CBCT was established at 3.6 mm^3 for detection of lesions 0-10mm^3. Of the CBCT lesions determined by Amira software to be greater than 0 mm^3 but less than or equal to 3.6 mm^3 (designated as no PARL), 3/13 were detected as PARL by periapical radiography. The remaining 10 lesions detected by periapical radiographs all had a value of 0mm^3 using Amira software. Of these, 7 were identified in surgery cases and 3 in retreatment cases. If PA led to false positive interpretations, this could pose a potential problem for patients who receive recall examinations in facilities that do not have CBCT capability. Trends are detectable in which restorative dentists extract previously root canal treated teeth in which an apical radiolucency is identified, rather than referring the patient to an Endodontist for evaluation and treatment. Perhaps some of these teeth that might otherwise be extracted due to PA false positive detection could be retained.

Due to the retrospective nature of this study, healing rates reflect those of teeth that have survived the post-operative period for patients who returned for a recall examination. The recall rate for the patients treated from June 2011 to July 2015 was not determined. It is possible that patients who returned for a recall examination reflected a higher percentage of patients who were symptomatic at the time of recall and were seeking free corrective treatment in the Military Health System. If this occurred, this study may have artificially low healing rates.

Blinding of examiners was only partially possible as EMS recall images with root end resection and fill could be differentiated from the other 3 categories (EMS and retreatment pre-operative, and retreatment recall). We acknowledge possible implicit bias if examiners approached their task with a preference for one treatment modality over another. Examiners were instructed to provide interpretations and tracings in an objective manner.

Under the heading of "outcomes" The *American Association of Endodontists Glossary of Endodontic Terms (ninth edition, 2016)* defines four categories: 1) "*Healed* – Functional, asymptomatic teeth with no or minimal radiographic periradicular (apical pathosis)", 2) "*Nonhealed* – Nonfunctional, symptomatic teeth with or without radiographic periradicular (apical) pathosis (radiolucency)", 3) "*Healing*- Teeth with periradicular (apical) pathosis (radiolucency), which are asymptomatic and functional, or teeth with or without radiographic periradicular (apical) pathosis (radiolucency), which are symptomatic but whose intended function is not altered)", and 4) "*Functional*- A treated tooth or root that is serving its intended purpose in the dentition." Taken together, each of these designations contain provision for a radiolucency at recall, which places the clinician in the position of subjectively categorizing a case by considering if a rarefaction is absent, minimal or otherwise. If CBCT PARL volume rendering gains prominence, greater clarity in our terminology will be possible with quantification of outcomes criteria. Each outcomes designation could then be tied to prudent course(s) of action, which is the ultimate utility of diagnostic terminology. Clarity of terminology and course of action are required if trends toward extraction of serviceable teeth in favor of implant placement are to be stemmed. We propose that for treated asymptomatic teeth with lesions that have reduced in size, but have not completely resolved, the term "Reductive Healing" be utilized instead of the term "healing." This will more clearly differentiate cases that have an asymptomatic reduction in PARL from cases where PARL has remained unchanged or increased in size. We suggest that the clinical course of action indicated by an outcome designation of Reductive Healing is a recall interval based on best evidence, clinician experience and patient desires.

With further studies documenting the histological nature of tissue present in lesions that have reduced in size (as detected by CBCT), but not fully resolved, it may be possible to designate an acceptable volume for PARL which represents a healed state. This would allow further refinement and definition of outcomes assessment terminology and recommended treatment.

Conclusion:

In this CBCT and clinical data-based outcomes assessment EMS resulted in greater mean volumetric reduction and a higher healing rate compared to retreatment. Post-operative CBCT is more sensitive and specific than PA in assessing PARL and has demonstrable utility in outcomes assessment. These findings suggest that in the future, volume rendering can be incorporated into outcomes assessment, and terminology and treatment recommendations can be refined.

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The authors have no conflicts of interest related to this study.

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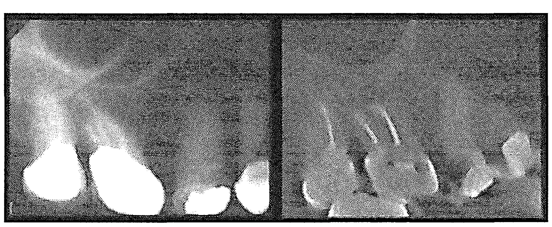


Figure 1. At 32 months post-apical surgery, the PA on the left indicates no apical radiolucency associated with tooth #2. In contrast, the CBCT image on the right was taken on the same date and clearly indicates a PARL associated with the MF and DF roots of tooth #2.

Table 1. 95% CL for various PARL volume ranges. Note, PARL measuring 3.6mm³ or less are counted as 0 mm³ (no PARL).

Volume Range (mm)	# Images in each volume range	# Images retraced in each volume range	95% CL (mm)
0.1 -10	51	2	± 3.6
0.1 - 25	83	4	± 4.0
26-100	50	3	± 10.8
101-200	26	4	± 15.4
201-1500	16	7	± 31.6

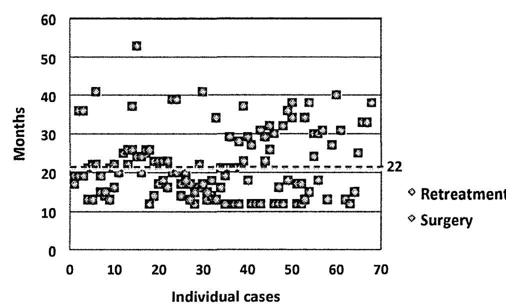
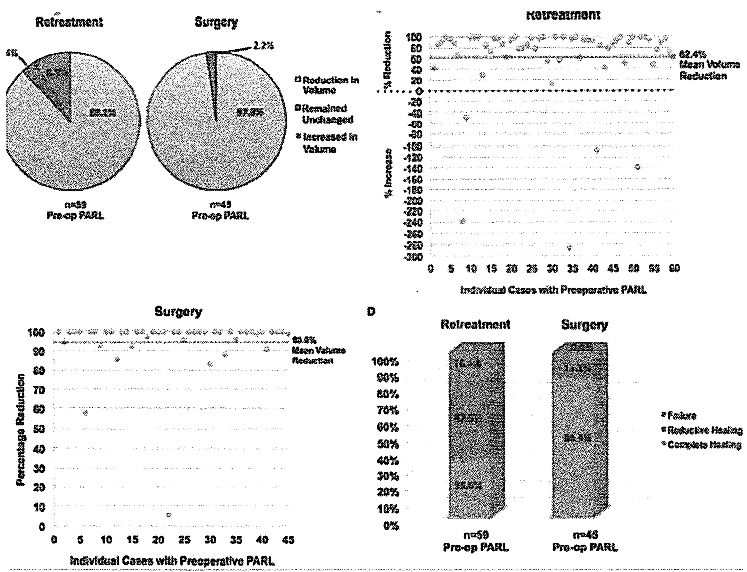


Figure 2. Mean Follow-up Period for Retreatment and Endodontic Microsurgery Cases.



ure 3. *(A)* Percentage of teeth with pre-operative PARL in which a PARL increased in size, decreased in size, or remained unchanged. *(B-C)* PARL ume reduction per tooth. *(D)* Outcome of teeth with pre-operative PARL based on volumetric changes in PARL and clinical findings.